IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

GB
AP

In re patent application of:

BERGMANN, *et al.*

Appl. No.: 09/806,437

Filed: March 30, 2001

For: METHOD AND SUBSTANCES FOR DIAGNOSIS AND THERAPY OF SEPSIS AND SEPSIS-LIKE SYSTEMIC INFECTIONS

Art Unit: 1646

Examiner: Brannock, M.

Atty. Dkt. 11377/279277

Amendment to Comply With Sequence Listing Rules

Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Notice to Comply with Requirements dated September 5, 2002, Applicants are submitting the following amendments and remarks to comply with the Sequence Listing rules.

Amendments

B1

Please enter the Sequence Listing enclosed herewith on separate pages following the claims and abstract of the application.

On page 2-3 of the specification, please amend paragraph that starts on line 32 of page 2 and ends on line 20 of page 3 to read as follows:

B2

Regarding the nature of the peptide determined as "procalcitonin" in sepsis, it was in fact made clear from the outset in the above-mentioned patients that the specific peptide need not be completely identical to the known procalcitonin peptide of full length, which is formed in the thyroid glands as a calcitonin precursor. However, the

question as to whether the procalcitonin formed in the case of sepsis differs from the procalcitonin formed in the thyroid glands remain unanswered to date. Possible differences were posttranslational modifications of the known procalcitonin, such as glycosylations, phosphorylations or modifications of the primary structure, but also modified, shortened or lengthened amino acid sequences. Since the analytical assay methods used to date did not reveal any differences between the procalcitonin known as the calcitonin precursor and the procalcitonin formed in the case of sepsis, it was provisionally generally assumed that the procalcitonin formed in the case of sepsis is identical to the calcitonin precursor and is thus a peptide having the known procalcitonin sequence of 116 amino acids (procalcitonin 1-116). **(SEQ. ID. NO: 1)**

B2

On page 3-4 of the specification, please amend paragraph that starts on line 31 of page 3 and ends on line 5 of page 4 to read as follows:

B3

The starting point for the invention disclosed in the present Patent Application is the surprising discovery that the procalcitonin detectable in comparatively high concentrations in the serum of patients in the case of sepsis and sepsis-like systemic infection is not the complete procalcitonin 1-116 comprising 116 amino acids but procalcitonin shortened at the amino terminus by a dipeptide but otherwise identical and having an amino acid sequence of only 114 **(SEQ. ID. NO: 3)** amino acids (procalcitonin 3-116).

On page 4 of the specification, please amend paragraph that starts on line 6 to read as follows:

B4

The dipeptide missing in comparison with the complete procalcitonin has the structure Ala-Pro. The lack of a dipeptide comprising a proline residue as a second amino acid **(SEQ. ID. NO: 2)** of the amino terminus of the complete procalcitonin sequence led to the presumption that a specific peptidase might play a role in the production of the procalcitonin 3-116 detectable in the case of sepsis, that is to say the so-called dipeptidyl-(amino) -peptidase IV (DP IV or DAP IV or CD26).

On page 11 of the specification, please amend paragraph that starts on line 6 to read as follows:

B5

For the fractions 50- 52 , in which the predominant procalcitonin immunoreactivity was to be found, it emerged that the peptides contained therein clearly have the following N-terminus (15 amino acids) :

Phe Arg Ser Ala Leu Glu Ser Ser Pro Ala Asp Pro Ala Th r Leu

(SEQ. ID. NO: 4)